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Health and Economic Consequences of Sevelamer Use for Hyperphosphatemia in Patients on Hemodialysis

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ABSTRACT

Objectives: The safety and efficacy of sevelamer hydrochloride in binding phosphate in patients with end-stage renal disease and its ability to attenuate the progression of cardiac calcification have been well documented but not the longer-term health and economic implications. Thus, a model of the predicted long-term consequences of sevelamer compared with calcium-based binders (acetate and carbonate) was developed.

Methods: Long-term cardiovascular implications of 1 year of treatment with phosphate binders in patients on hemodialysis are estimated based on the patient's demographics, comorbidities, and physiologic and renal parameters. The initial calcification score and expected changes over 1 year are derived using regression equations developed from the Treat-to-Goal study and translated to cardiovascular disease risk based on equations developed from a long-term cohort study. In this article, the implications of cardiovascular disease for life expectancy and medical costs are accounted for from a US payer perspective.

Results: The cardioprotective effect of sevelamer over 1 year is estimated to result in a 12% reduction in cardiovascular events compared with calcium acetate. In a population of 100 patients, the savings of $205,600 accrued due to avoiding nine cardiovascular events with sevelamer, largely offset the increased binder costs, leading to a favorable cost-effectiveness ratio of about $2200 per (discounted) life-year gained.

Conclusions: Although both binders provide equivalent phosphate binding capacity, the results indicate that the advantage of 1 year of treatment with sevelamer in attenuating the progression of calcification has important clinical and economic consequences, suggesting that this provides good value for money.

Keywords: cardiovascular events, cost-effectiveness, end-stage renal disease, phosphate binders.

Introduction

Chronic renal failure is a functional diagnosis characterized by a progressive decrease in glomerular filtration rate, eventually reaching end-stage renal disease (ESRD) requiring dialysis or transplantation for the patient's survival. In 2001, there were more than 360,000 patients in the United States with ESRD and the number of patients needing chronic dialysis has been increasing at a rate of 9% per year [1,2]. These patients suffer cardiovascular events more frequently than expected and this has been shown to be associated with both atherosclerotic plaques and stiffening of arterial walls [3]. Because coronary calcium is frequently seen in these atherosclerotic lesions, its detection has been taken to be the direct imaging of atherosclerosis [4]. Although still controversial, evidence supporting the independent predictive value of imaging with electron beam tomography (EBT) has been accumulating in the general population [5–11].

There is compelling evidence of increased prevalence of cardiac calcifications in ESRD, especially after long-term dialysis, but the precise pathogenesis and clinical significance remain to be elucidated [12,13]. Several factors likely contribute to the predisposition to widespread calcification in ESRD. Some of these risk factors are the well-established ones associated with coronary artery disease in the general population (e.g., hypertension, diabetes, dyslipidemia), whereas others are specific to ESRD patients. The metabolic abnormalities present in ESRD lead to an increasingly disordered calcium and phosphate metabolism. As renal function deteriorates, calcium excretion is impaired and excess calcium is transported into cellular and interstitial compartments. Although this helps maintain cal-

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cium homeostasis, it predisposes the patient to vascular calcification [14]. This process is exacerbated in those on hemodialysis by calcium absorption from dialysate, abnormalities in bone buffering and turnover, and ingestion of calcium-based phosphate binders to treat hyperphosphatemia [15]. The hypothesis that the process of calcification may be favorably altered by using a noncalcium based binder is supported by several studies that have found that the amount of calcium ingested daily as a phosphate-binding agent is significantly associated with higher vascular calcification scores [16–18].

In 1998, sevelamer hydrochloride (Renagel), a nonmetal, noncalcium polymer that binds preferentially to phosphate through ion exchange and hydrogen bonding in the duodenum, was shown to be safe and effective in binding phosphate in patients on hemodialysis [19]. More recently, sevelamer has also been shown to attenuate the progression of coronary and aortic calcification—evaluated using EBT—over a 1-year period relative to calcium binders (Treat-to-Goal [TTG] study) [20,21].

In this article, we present a clinical-economic model that brings together the best available information on the risks associated with calcification over the longer term and their clinical and economic consequences to advance a more rigorous and complete understanding of the choice of phosphate binder. The analyses presented here are specific to the United States, but the model is designed to be applicable in a variety of health-care systems around the world. The customized analyses facilitated by this model should allow decision-makers to assess the consequences associated with the choice of phosphate binder for their particular patient population or setting, while remaining within the bounds of the efficacy demonstrated in the TTG study.

Methods

Disease Simulation Model Overview

The main model modules and key linkages are shown in Figure 1. In essence, the selection of phosphate binder and patient characteristics at the start of treatment drive the changes in calcification score expected over the course of 1 year. The impact of these 1-year changes on cardiovascular risk, as well as on the clinical and economic sequelae, is estimated in the final module.

The model functions as an individual patient simulation, implemented using discrete event simulation—a modeling technique that permits the course of disease and its management to be conceptualized in terms of the events that happen and the impact these have on the patients and other components of the system [22,23]. All relevant aspects can be incorporated explicitly and efficiently, and the entire model can be presented very transparently. In a discrete event simulation, there is no specific cycle length. That is, time passes specific to the experience of a particular patient at a given point in time. This permits flexibility and efficiency not allowed by other modeling approaches.

A schematic representation of the model structure is provided in Figure 2. At the start, a patient with ESRD is assigned characteristics based on prespecified distributions for demographics, physiologic parameters, renal parameters and comorbidities. The initial calcification score (EBT Agatston score [24]) is also assigned. These assignments take place by weighted random sampling of the distributions. An identical copy of each patient is then

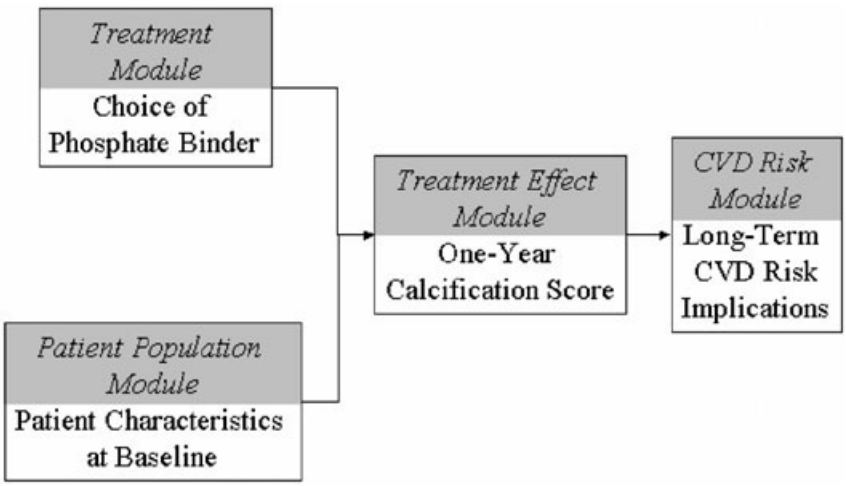

Figure 1 Relationship among the key modules of the Disease Simulation Model. CVD, cardiovascular disease.

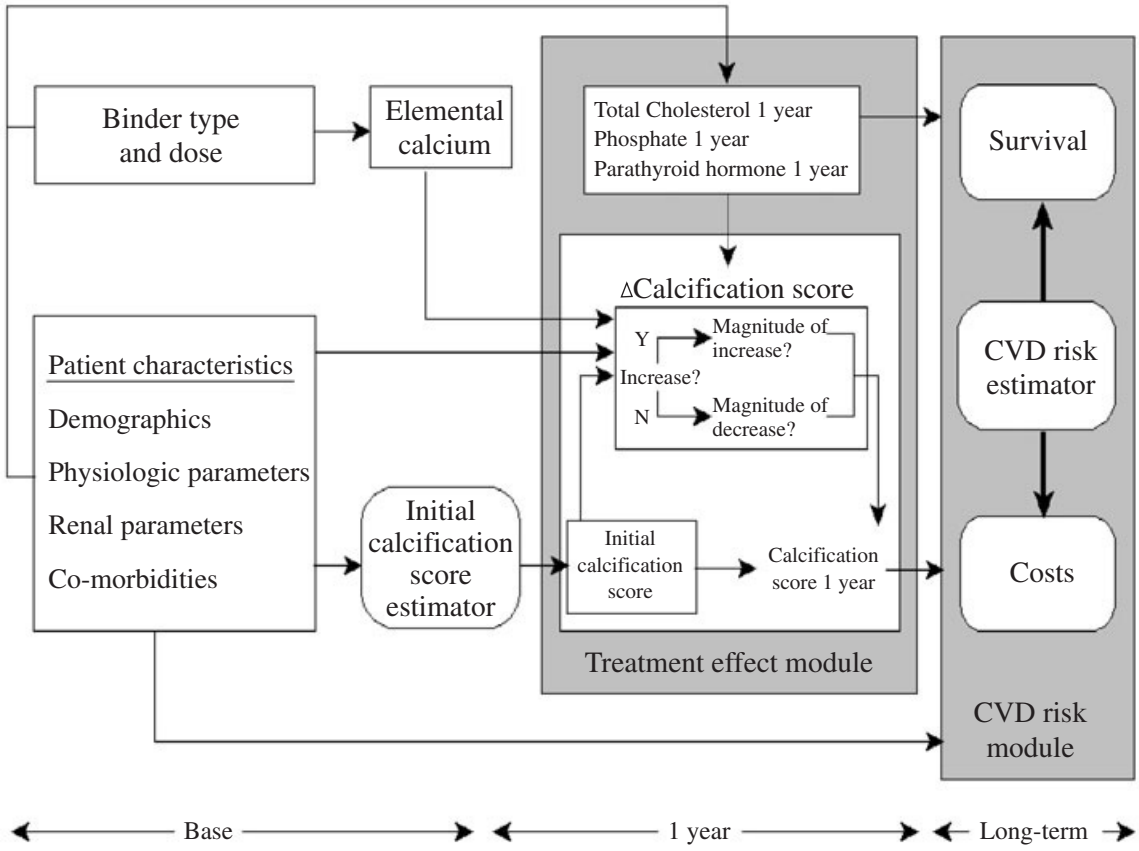

Figure 2 Simplified structure of the Disease Simulation Model. CVD, cardiovascular disease.

created. This is done to ensure that factors other than type of phosphate binder do not create nuisance variance—it is equivalent to carrying out an identical twin study. One of the twins is assigned sevelamer treatment and the other a calcium-based binder (i.e., as if there were perfect treatment randomization). The changes in cardiac calcification, physiologic and renal parameters expected to occur given the patient's assigned treatment are then derived using regression equations developed from the TTG study. For these analyses, three sets of calculations were done corresponding to 1 year of treatment with sevelamer, and with each of the two calcium-based binders.

The long-term—up to lifetime—implications of these 1-year changes in calcification and other parameters are then estimated in terms of the occurrence of cardiovascular disease, which is simulated based on the patients' calcification score and other characteristics at the end of the treatment year. During this time, cardiovascular disease events are counted and management costs are accumulated. The implications of cardiovascular disease for life expectancy are also accounted for. The base case analysis is expressed over 13 years because the majority of patients have died by then. Cost and benefits occurring beyond 1 year are discounted at 3% per year. The modeling process is replicated for a hypothetical cohort of 10,000 patients. The calculations are carried out using ARENA, a software package that facilitates discrete event simulations coded in SIMAN language [25].

Treatment Effect Module

The effect of phosphate binders on the progression of coronary and aortic calcification has been documented in TTG using EBT technology. Changes in EBT calcification scores over time are therefore the main drivers of the treatment effect in the model. To enable application of the TTG study findings to populations with ESRD differing from those of TTG in terms of demographics and disease characteristics, regression analyses were conducted to predict changes in calcification by treatment group over the course of 1 year, rather than directly implementing the changes observed in the trial. A two-part model was developed for that purpose. First, a logistic regression analysis was carried out to pro-

Table 1 Regression analyses for change in calcification score over time

	Logistic regression		Multiple linear regression			
			Ln (EBT increase)		Ln (EBT decrease)	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Binder type (sevelamer/calcium)	0.45 (0.18)	0.011				
Calcium × Phosphate ($mmol^2/L^2$)	–0.27 (0.14)	0.062				
Albumin (g/L)	0.08 (0.07)	0.272	–0.08 (0.06)	0.206		
Ln (EBT)	–0.12 (0.06)	0.059	0.34 (0.12)	0.007	1.06 (0.11)	<0.0001
Elemental calcium (mg)			1.25E-05 (0.5E-05)	0.015		
CVD history (no/yes)			–0.32 (0.17)	0.073		
Sex (male/female)			–0.32 (0.14)	0.035	–0.37 (0.15)	0.018
Race (non-Caucasian/Caucasian)					–0.72 (0.17)	<0.0001

The logistic regression analysis provides the probability a patient will have an increase in calcification score during the course of 1 year. The linear regression equations predict the magnitude of the change in calcification score. The smearing estimators to be used when retransforming the predicted log changes are 1.357 for the increase model and 1.375 for the decrease model. The –2LogL χ^2 for the logistic regression model is 14 (4 df), $P = 0.006$. The model F for the increase model is 10 (5 df), $P < 0.0001$, $R^2 = 0.56$; for the decrease model 42 (3 df), $P < 0.0001$, $R^2 = 0.75$.

vide the probability that a patient will have an increase in calcification score during the course of 1 year. Then, linear regression analyses were conducted to predict the magnitude of the change in calcification score (increase and decrease considered separately). The final models are summarized in Table 1.

In TTG and other trials, a beneficial effect of sevelamer on cholesterol lowering has also been observed [26]. This treatment effect is applied in the model, assuming no difference between the groups with respect to the use of cholesterol-lowering treatments, as specified in the TTG protocol. The implications of altering this assumption are examined in sensitivity analyses. Although a beneficial treatment effect was also observed in terms of oversuppression of parathyroid hormone, it was not modeled because of lack of consistent data on the consequences of oversuppression (e.g., fractures). As documented in the clinical trial, no difference in phosphate binding capacity is assumed among the treatment groups (i.e., binder dose is adjusted to achieve desired binding capacity).

Cardiovascular Disease Risk Module

Survival. A Gompertz function, which has been shown to be a good estimator of general human mortality [27], was used to estimate the death hazard over time:

$$\lambda_{(t)} = -\lambda_0 e^{\gamma t} \quad (1)$$

where λ_0 is the hazard at time 0 (beginning of dialysis) and γ is the accelerator. Both parameters were estimated using information from the US Renal Data System (USRDS) annual report [2], which provides up to 10-year survival data adjusted for age for all incident dialysis patients. Duration of life is not adjusted by quality of life, because of a lack of data documenting the incremental effect of cardiovascular disease on the quality of life of patients with renal failure.

Cardiovascular disease risk estimator. Patients' risk for initial and subsequent cardiovascular events was estimated through implementation of a set of regression equations developed based on a longitudinal data set of 179 patients with ESRD treated at one center in France—subgroups of this population have been used in previous analyses [28]. Patients entered the data set some time after dialysis start and follow-up ended at kidney transplant, death, move, or April 2002. This data set has been described elsewhere [29]. Briefly, information was available on calcification and other patient characteristics (including biochemistry values during the prior year) and on the occurrence of five cardiovascular event types over time: congestive heart failure, coronary artery disease, cerebrovascular disease, aortic disease, peripheral arterial disease. The EBT score corresponding to the measured Doppler score was estimated using an equation derived from TTG (Table 2).

A Cox proportional hazards analysis was conducted to identify the determinants of cardiovascu-

Table 2 Multiple linear regression analysis predicting the logarithmically transformed EBT score

Variable	β (SE)	*P* value
Age (year)	0.02 (0.01)	0.013
Dialysis vintage (>36 months/≤36 months)	0.35 (0.11)	0.002
Serum calcium (mmol/L)	1.42 (0.73)	0.053
Serum phosphate (mmol/L)	0.39 (0.21)	0.061
Total cholesterol (mmol/L)	–0.16 (0.10)	0.117
HDL-cholesterol (mmol/L)	–0.54 (0.30)	0.077
CVD history (no/yes)	–0.70 (0.12)	<0.0001
CVD history × age	0.01 (0.01)	0.139

Because the distribution of baseline EBT calcification scores was quite skewed, the values were logarithmically transformed to achieve a normal distribution and permit use of standard parametric statistical tests. The smearing estimator equals 1.847. The model F is 12 (8 df), $P < 0.0001$, $R^2 = 0.40$.
CVD, cardiovascular disease.

Table 3 Event type breakdown for nonfatal and fatal cardiovascular events

	Nonfatal events		
	Initial (%)	Subsequent (%)	Fatal events (%)
Peripheral arterial disease	33	50	5
Congestive heart failure	11	11	14
Coronary artery disease	47	32	57
Aortic disease	9	—	5
Cerebrovascular disease	—	7	19

lar risk [29]. The final regression model includes the EBT score, diabetes, C-reactive protein levels, diastolic blood pressure, sex, smoking, hypertension, and total cholesterol. The individual patient's hazard can be derived as:

$$h_0^i = h_0 \times HR^i \quad (2)$$

For consistency with the mortality data, a Gompertz function was used to extrapolate this base hazard over time. The same acceleration parameter γ as for mortality was used. The likelihood of a cardiovascular event being fatal is based on the longitudinal data set (22% for an initial and 41% for a subsequent event). The specific event type is assigned based on the observed distributions (Table 3). A patient that experiences a fatal event (cardiovascular or other) is removed from the model once the respective costs and life-years have been accumulated. In case of a nonfatal cardiovascular event, the patient's time-dependent risk of a subsequent cardiovascular event is estimated using a Weibull function:

$$\lambda_t = \frac{\gamma}{\alpha}\left(\frac{t}{\alpha}\right)^{\gamma-1} \quad (3)$$

where γ and α are estimated at 0.658 and 941.553 [29,30].

After 1 year, the relevant physiologic parameters (i.e., calcification score, total-cholesterol, serum phosphate, parathyroid hormone) of survivors who have not suffered an event are updated and the cardiovascular risk is computed given these new characteristics (Fig. 3).

Costs

The direct medical costs, from the perspective of a payer providing full health-care coverage in the United States, are reported in 2002 US dollars. Where 2002 values were not available, older values

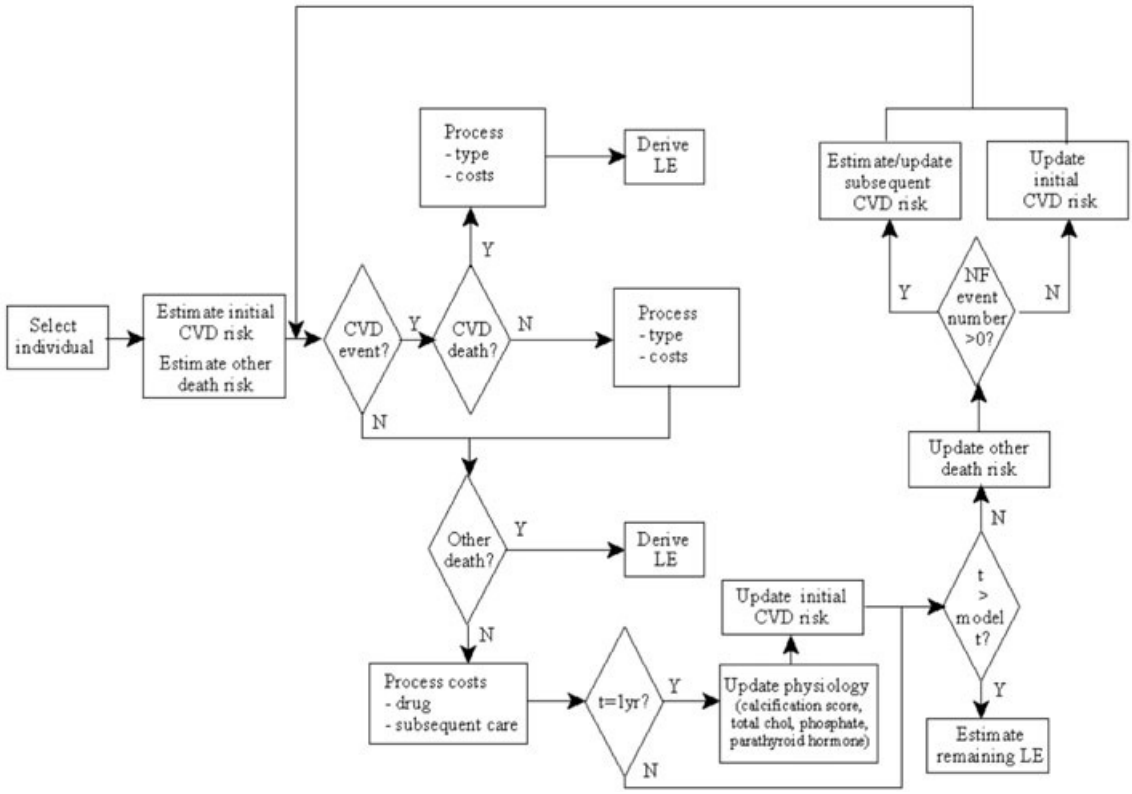

Figure 3 Schematic representation of the Cardiovascular Disease Risk Module. CVD, cardiovascular disease; LE, life expectancy; *t*, time in model; model *t*, model time horizon; NF, nonfatal.

were inflated using the medical care component of the US Consumer Price Index. Charges were adjusted by means of a cost-to-charge ratio of 0.61 established by the Massachusetts Office of Health Care Finance and Policy [31].

Hospitalization. Inpatient resource-use data and costs (all accommodations, special care unit, pharmacy, laboratory, imaging, diagnostic and surgical procedures) were derived from all-payer 1999 acute inpatient hospital discharge databases from California, Florida, Maryland, Massachusetts, and Washington (Table 4) [32–36]. Cases were identified by means of principal ICD-9 diagnosis codes corresponding to the five cardiovascular events of interest (congestive heart failure, coronary artery disease, cerebrovascular disease, aortic disease, peripheral arterial disease) and secondary diagnosis of chronic renal failure. Physician resource-use profiles were developed for each diagnosis based on length of stay, diagnosis and procedure codes, use of the emergency room and intensive care unit, dialysis during the hospital stay and discharge status, and the corresponding costs were calculated using pertinent Physicians' Current Procedural Terminology codes [37,38].

Subsequent care. For patients discharged home, no further costs are included. Costs per episode of home health care ($2494), inpatient rehabilitation ($13,722), skilled nursing facility ($8289), and intermediate care facility ($34,264) were applied to the proportions of patients using them [32–36,38–40].

Medications. The 2002 Wholesale Acquisition Cost was used as the cost for sevelamer ($1.2799/g) and calcium acetate ($0.1766/g for PhosLo™ 667 mg tabs). The price used for calcium carbonate equals €10.46 (100 Sertürner 500 mg tabs) [41], or approximately $0.2054/g. A weighted average daily cost was calculated for cholesterol-lowering drugs using the distribution of use observed in TTG: $3.63 [42].

An overview of the main model parameters and their source is provided in Table 5.

Validation

To assess the face validity, the model structure was presented to two scientific advisory boards, one consisting of clinical experts from Brazil, France, the UK, and the United States, and another of economists experienced in this type of modeling from Brazil, Germany, the UK, and the United States. To test the technical validity of the model, validation analyses were carried out. These involved setting inputs to extreme values and checking for logical consistency. In addition, calibration analyses compared the outputs to the inputs from TTG to ensure that the model faithfully replicated the trial.

Analyses

The characteristics of the patient population used for the base case are summarized in Table 6. The base case compares sevelamer with calcium acetate because this is by far the most widely used calcium-based binder in the United States. The findings for calcium carbonate are explored in a sensitivity analysis. Apart from estimating the costs and health consequences of treatment, cost-effectiveness ratios (CERs) reflecting the cost per (discounted) life-year gained (dLYG) and per cardiovascular event averted were also derived.

Univariate sensitivity analyses considered the impact of sevelamer on the progression of calcifi-

Table 4 Acute hospital costs and discharge disposition status by analysis population

	Acute hospital costs ($)	Discharge disposition status				
		Home (%)	HHC (%)	Rehab facility (%)	SNF (%)	ICF (%)
Peripheral arterial disease	23,071	43	15	9	26	7
Alive at discharge	22,161					
Died in hospital	38,349					
Congestive heart failure	11,326	64	17	2	14	3
Alive at discharge	10,723					
Died in hospital	16,995					
Coronary artery disease	21,247	65	17	3	12	3
Alive at discharge	20,155					
Died in hospital	27,923					
Aortic disease	45,433	57	14	7	21	1
Alive at discharge	39,394					
Died in hospital	83,481					
Cerebrovascular disease	11,247	47	14	9	24	6
Alive at discharge	10,456					
Died in hospital	16,508					

HHC, home health care; ICF, intermediate care facility; SNF, skilled nursing facility.

Table 5 Summary description of the main model parameters

Main model parameters	Source, ref
Treatment effect	
Two-part multivariate regression model to predict changes in EBT over the course of 1 year	[20]
Change in physiologic parameters during year of treatment	
Linear regression models to predict changes in total cholesterol and parathyroid hormone levels	[20]
All patients assumed to achieve target serum phosphate level of 1.776 mmol/L	[20]
Non-CVD and all-cause (used to estimate remaining life expectancy for patients alive at the end of the model time horizon) mortality	
Gompertz function	[2,29]
Risk for initial CVD events	
Population base hazard h_0	[29]
Individual patient hazard ratio (HR^i) derived from Cox proportional hazards model	[29]
Gompertz function to extrapolate risk over time	[2]
Risk for subsequent CVD events	
Weibull function	[29]
Proportion of fatal CVD events	[29]
CVD event type distribution	[29]
Hospitalization costs	[32–36,38]
Subsequent care	
Location of care on discharge from hospital	[32–36]
Costs per episode of home health care, inpatient rehabilitation, skilled nursing facility, intermediate care facility	[32–36,38,39,40]
Medications	
Renagel and calcium acetate Wholesale Acquisition Cost	Genzyme Corporation
Calcium carbonate—Yellow List	[41]

cation, the effect of calcification on cardiovascular risk, cholesterol-lowering treatment practices, the treatment cost, the cardiovascular event costs, the model time horizon, the discount rate, and future medical costs. An analysis was also conducted to explore how long the risk reduction afforded by 1 year of treatment would have to last for a given cost-effectiveness threshold to be met. Results of multivariate sensitivity analyses are also presented.

All results are based on 10 replications of 10,000 patients.

Results

Base case

After 1 year of treatment with sevelamer, 36% of patients are expected to have an increase in EBT, compared with 57% of those on calcium acetate. The mean calcification score decreases from 1502 to 1362 in the sevelamer group compared with an increase to 1557 in those on calcium acetate. After 1 year, patients treated with sevelamer are thus expected, on average, to have a 13% lower calcification score than patients treated with calcium acetate. The results are summarized in Table 7.

In a population of 100 patients, 33 of those receiving sevelamer are expected to experience an initial cardiovascular event (fatal: 8), compared with 37 of those who receive calcium (fatal: 8). A total of 32 subsequent events (fatal: 13) occur while on sevelamer treatment, compared with 37 (fatal: 16) on calcium. Sevelamer is thus estimated to prevent a total of nine events, which represents a 12% reduction in cardiovascular risk. Therefore, 11 patients need to be treated for 1 year to prevent one cardiovascular event.

The majority of the total cost for each treatment option is attributable to hospital inpatient management of cardiovascular disease (74% for sevelamer; 86% for calcium acetate), followed by subsequent in- and outpatient care (10% and 11%, respectively). The expense of 1-year of sevelamer therapy contributes 15% to the overall cost, compared with 2% for calcium. HMG-CoA reductase inhibitors make up the remaining 2% of the cost in both groups. As can be seen, the 12% decrease in cardiovascular disease management cost due to avoiding nine events with sevelamer (savings of $205,600) largely offsets the increased binder costs, leading to a favorable CER of less than $2500 per discounted LYG and around $4500 per event prevented.

Sensitivity analysis

The results improve further when comparing sevelamer to calcium carbonate: $1107/dLYG and $2262 per event prevented; mainly because of the higher daily calcium consumed by these patients. As illustrated in Figure 4, the cost-effectiveness of sevelamer was very sensitive to the model time horizon. The CER is $111,000/dLYG at 2 years, drops quickly to around $50,000/dLYG at 3 years, and

Table 6 Characteristics of the patient population for the base case analysis

Patient characteristics*	Mean or %	Interquartile range
Demographics		
Age (years)	54	40–67
Sex (males)	60%	
Race (white)	85%	
Smoking (smokers)	6%	
Physiologic parameters		
Total cholesterol (mmol/L)	4.75	3.95–5.50
HDL cholesterol (mmol/L)	1.16	0.90–1.36
Diastolic blood pressure (mm Hg)		
Hypertension	85	74–95
No hypertension	73	64–81
Renal parameters		
Serum phosphate (mmol/L)	1.84	1.52–2.15
Serum calcium (mmol/L)	2.34	2.25–2.44
Parathyroid hormone (pg/ml)	318	80–436
Vintage (months)		
Diabetes	28	10–24
No diabetes	79	16–120
Comorbidities		
Diabetes by age group (year)		
≤29	0%	
30–49	2%	
50–64	23%	
≥65	18%	
Hypertension by sex		
Males	80%	
Females	63%	
CVD history by diabetes and age		
Diabetes (year)		
≤29	0%	
30–49	46%	
50–64	73%	
≥65	88%	
No Diabetes (year)		
≤29	3%	
30–49	11%	
50–64	31%	
≥65	58%	
Treatment		
Dose sevelamer (mg)	6136	3781–8607
Dose calcium acetate (mg)	4443	2549–5766
Dose calcium carbonate (mg)	3470	2651–4323
Baseline EBT calcification score	1500	79–1652

*Because the longitudinal data set reflects an actual practice of patients on hemodialysis, which should be more generalizable than a clinical trial population, these data were used to define the population used in the base case analysis. Only a few exceptions were made. Because the high proportion of smokers observed in the French data set (51%) was not considered to be an accurate reflection of current smoking habits in the United States, the proportion of smokers observed in TTG was used instead. For consistency, the values for total cholesterol, HDL cholesterol and parathyroid hormone were also obtained from TTG. Correlations between the input parameters were formally assessed in both the longitudinal and TTG data set, and those that were statistically significant and clinically relevant were incorporated in the model. C-reactive protein (correlated with age and cardiovascular history) and albumin (correlated with age and C-reactive protein) are not included in the table because they are derived using regression equations with the intercept sampled from a normal distribution to recreate the variability observed in the source data.

stabilizes at around $2,500/dLYG from year 12 onwards. Another relatively influential parameter is the impact of treatment on cardiac calcification. Sensitivity analyses were carried out using the 95% confidence interval (CI) of the β-coefficient for binder type in the logistic regression equation predicting increase versus no increase in EBT, as well as for the dose of elemental calcium in the linear regression equation predicting the magnitude of the increase. Use of the lower bound of the 95% CI results in a CER around $10,000/dLYG when only one of the coefficients is varied at a time. When both β-coefficients are changed simultaneously, using the lower bound of the 95% CI yields a CER around $20,000/dLYG. Using the upper bound always results in cost savings making sevelamer dominant over calcium treatment. When allowing cholesterol-lowering treatment practice to be altered from the prevailing practice in TTG by assuming that all patients with an LDL-cholesterol level >2586 mmol/L (>100 md/dL) will receive treatment per the K/DOQI guidelines, the CER changes to $9664/dLYG, mainly driven by the nondifferential 1-year cholesterol levels (i.e., assuming that statin treatment is at least as effective as sevelamer). The costs of hospitalizations often vary as a result of factors such as geographic region, access to health-care services, and payer. The costs of subsequent care for patients with ESRD who have suffered a cardiovascular event are difficult to estimate precisely as a result of lack of data. The stability of the results when varying the overall event cost—hospital and subsequent care combined—over a broad range (50% in either direction) was therefore assessed. Reducing the management cost by half results in a net cost of $1407 (CER: $8088/dLYG), whereas increasing the costs leads to savings of $649. For the other parameters tested, the CER remained well below $5000/dLYG.

Although it remains controversial whether to include future costs for unrelated medical care and nonmedical expenditures within economic evaluations, some researchers suggest they should be included on methodological grounds. We examined this issue using the total Medicare payments for patients on hemodialysis per patient year at risk as the estimate for the annual future cost for medical care [2], and predicted an increase in cost per dLYG to around $59,000.

Given the need for phosphate binders as long as patients are on hemodialysis, clinicians and other decision-makers might legitimately ask about the longer-term implications of sevelamer use. Until long-term trial or observational data are available and there is more insight into the biological mechanisms of calcification and cardiovascular risk, this cannot be estimated with any confidence. Instead, we explored the issue by estimating how long the risk reduction obtained by 1 year of treatment has to last in order for a given cost-effectiveness thresh-

Table 7 Results of the cost-effectiveness analysis (base case)

	Sevelamer	Calcium acetate	Difference
One-year EBT	1,362	1,557	−195
CVD events (per 100 patients):	65 (21 F)	74 (24 F)	−9
Peripheral arterial disease	17 (1 F)	20 (1 F)	−2
Congestive heart failure	7 (3 F)	8 (3 F)	−1
Coronary artery disease	32 (12 F)	36 (14 F)	−4
Aortic disease	3 (1 F)	4 (1 F)	0
Cerebrovascular disease	6 (4 F)	7 (5 F)	−1
Total costs ($)	18,113	17,734	379
CVD costs ($)	15,045	17,101	−2,056
Hospitalization costs ($)	13,323	15,166	−1,843
Subsequent care costs ($)	1,722	1,935	−213
Statin costs ($)	364	363	0.36
Treatment costs ($)	2,704	270	2,431
Life expectancy (year)	9.19	8.95	0.241
Life expectancy discounted (year)	7.61	7.43	0.178
Incremental cost-effectiveness, $/life-year gained			1,641
Incremental cost-effectiveness, $/discounted life-year gained			2,219
Incremental cost-effectiveness, $/CVD event prevented			4,448

CVD, cardiovascular disease; F, fatal.

old to be met (Fig. 5). For example, in order for 1 year of treatment with sevelamer to yield a CER below $25,000/dLYG, the reduction in cardiovascular risk would have to persist for at least 4.3 years. With a threshold of $100,000/dLYG, the benefit would only have to last for a little over 2 years.

The results of the multivariate sensitivity analyses are summarized in Figure 6. The cost-effectiveness acceptability curve represents the probability that sevelamer is cost-effective at all possible values of the maximum acceptable CER appropriate for decision-making. If the ceiling CER is $2500 per dLYG, there is a 51% chance that sevelamer is cost-effective. The likelihood of sevelamer being cost-effective, increases to 95% with a ceiling ratio of $10,000/dLYG. There is a 5% chance that sevelamer use would result in cost savings. It should be noted that possible structural changes in the cardiovascular risk functions over time—reflecting uncertainty in the treatment effect beyond 1 year—are not accounted for in these multivariate analyses resulting from lack of information. There is currently insufficient clinical information to permit quantification of the likely impact, even for exploratory purposes. Were these to be

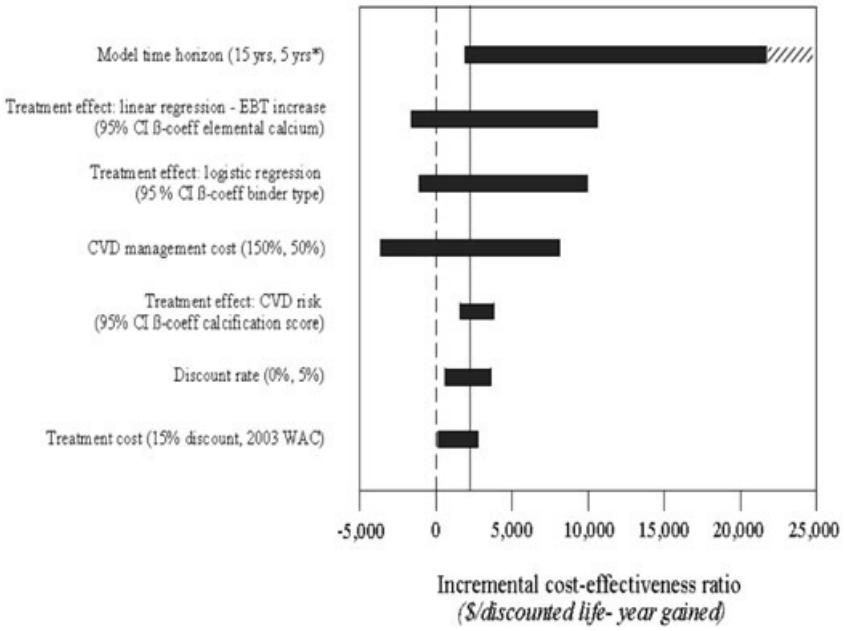

Figure 4 Univariate sensitivity analyses. The solid vertical line represents the incremental cost-effectiveness of treatment with sevelamer relative the treatment with calcium acetate when all variables were set at their baseline value. Horizontal bars indicate the range in incremental cost-effectiveness ratios obtained by setting each variable at the lower and upper limit of its range and holding all other variables constant at their baseline value. Incremental cost-effectiveness ratios less than $0 (dashed vertical line) indicate that treatment with sevelamer is cost-saving. (*: shorter time horizons are not depicted for clarity. 2 years: $111,000; 3 years: $53,000; 4 years: $33,000).

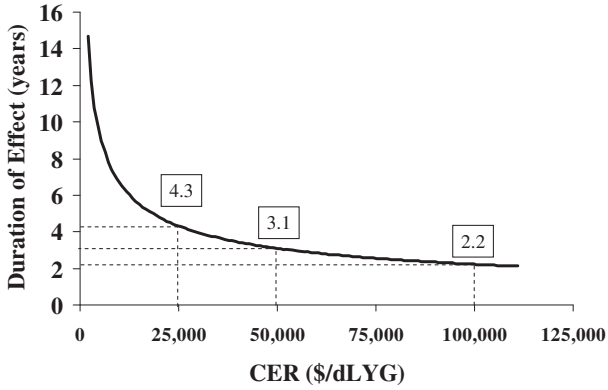

Figure 5 Analysis of the duration of benefit after 1 year of treatment required for a given cost-effectiveness threshold to be met.

considered, the uncertainty would undoubtedly increase considerably.

Conclusions

The ability to image and detect calcium deposition within the vasculature is a recent development. Thus, much remains to be learned about the implications of these lesions, particularly their quantitative relation to cardiovascular risk. Nevertheless, it seems prudent given the evidence accumulating in various populations to consider it undesirable to allow calcification to build. This is particularly important in patients such as those with ESRD who are at very high risk for cardiovascular problems. Clearly, any external factor that further aggravates the complex metabolic dysfunction that promotes calcification in these patients should be viewed with concern. Because a major contributor is the additional calcium load due to the use of calcium-based phosphate binders, the introduction of a safe alternative that is inert in this respect is potentially very attractive. In this article, we examined the cost-effectiveness of one such option, sevelamer, based on the assumption that coronary calcification is a serious problem exacerbated by exogenous calcium.

In a population of patients with ESRD with a mean EBT score of 1500, sevelamer is estimated to prevent a total of about nine cardiovascular events and to save 18 life-years per 100 patients, at a cost-effectiveness relative to calcium acetate of less than $2500/dLYG. These results compare favorably to those from other economic analyses in both renal failure and prevention of cardiovascular disease. A review covering 1968 to 2000 found that the cost-effectiveness of center hemodialysis ranged from $55,000 to $80,000 per LYG. It also found that kidney transplantation has become more cost-effective over time, reaching a plateau at approximately $10,000 per life-year [43]. Common interventions for prevention of cardiovascular disease, such as smoking-cessation programs, use of aspirin, statins and tissue plasminogen activator, yield CERs ranging from $220 [44] to $32,700 [45] per life-year.

The results should be viewed in light of several important limitations of the model and the strength of the supporting data. Most importantly, this is not a model of homeostatic balance and its sequelae at the level of the individual patient. The treatment-specific changes in calcification score, renal and physiologic parameters and their implications for cardiovascular risk should only be interpreted at a population level. Data are insufficient to allow for a detailed simulation of the impact of various treatment regimens on renal homeostasis in a given patient.

The quantitative link between calcification and cardiovascular risk is based on the only study that has so far provided longitudinal data on this in patients with ESRD [16,28,29,46]. This link is consistent, however, with the findings from studies done in initially asymptomatic, low- to intermediate-risk individuals without ESRD [6–10]. For high-risk individuals, the relationship has been somewhat less clear, but it should be noted that the validity of this conclusion has been questioned

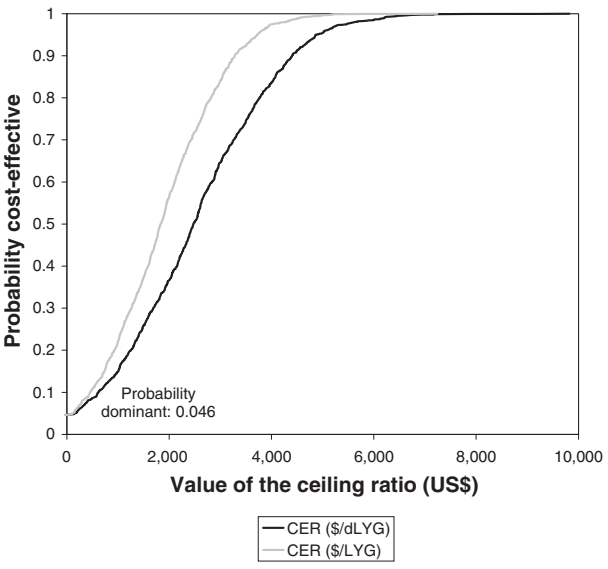

Figure 6 Cost-effectiveness acceptability curve. The curve was derived by simultaneously varying the treatment effect (95% CI for the β-coefficients in 1) logistic regression equation providing the probability a patient will have an increase in calcification score; 2) linear regression equation predicting the magnitude of the increase in calcification score; and 3) Cox-proportional hazards equation predicting cardiovascular risk) and the CVD management cost (±50%).

because of the imaging techniques used in that particular study [5,47].

The immediate effect achieved with 1 year of sevelamer treatment is a change in risk, specifically cardiovascular disease risk. One possible—and in fact the easiest—approach would be to stop here and present this change in risk to decision-makers as the return for the money spent on sevelamer treatment for their patients. Nevertheless, it is clinically relevant to try and translate this treatment effect into outcomes that are important to clinical and economic decision-makers. This is accomplished by examining how the risks will manifest over time, which is tantamount to integrating the risk curves. This approach is similar to the one typically used in cost-effectiveness analyses to translate the health effects established in clinical trials—which are nearly always too short-term for estimating survival—to the change in the full survival curve [48]. Because it is currently unknown how the absolute risk difference obtained after 1 year of treatment will evolve with continued treatment with either type of phosphate binder, it would be tenuous to make any projections about the expected treatment effect in terms of coronary calcification beyond TTG's time horizon—especially in view of the complex and multifactorial nature of the underlying disease processes. By strictly remaining within the bounds of the efficacy demonstrated in the trial, the only presumption made about future effect is that the predictive ability of the calcification score is not itself affected by treatment—in other words, that the impact of a change in score is correctly reflected by the respective failure-time curves for the two scores. This type of assumption is commonly required when intermediate outcomes are used (blood pressure reduction and lipid lowering are salient examples). Although it seems reasonable to assume that the outcomes implied by score changes brought about by treatment will be borne out, only long-term data can demonstrate this conclusively.

The predicted changes in EBT scores are based on the only data currently available: one clinical trial in 200 patients. Confidence in the model findings would strengthen if the beneficial effect of sevelamer on arterial calcification were confirmed in additional studies, ideally with even longer time horizons.

The economic implications estimated in this study are conservative in that only acute inpatient costs and the costs of subacute care provided immediately on discharge from the hospital are included for the management of cardiovascular events. There were insufficient data to reliably estimate the incremental costs associated with longer-term outpatient management of cardiovascular problems in patients with ESRD who are already receiving intense care. Consideration of only the cardiovascular implications associated with the choice of phosphate binder further contributes to the conservative nature of the estimates. For example, the consequences in terms of fractures and vascular access problems are not included. Indeed, in a study comparing patients on sevelamer to controls not receiving this binder, a 50% reduction was observed in all-cause first hospitalization over 17 months of follow-up leading to an annual savings of more than $16,500 per patient, on average [49].

Because the model was implemented as a discrete event simulation, it provided a means to more realistically represent health-care processes and, in turn, to better address the specific research questions posed without forcing the analyst to accept unnecessary compromises, which exact a heavy price in efficiency, transparency and credibility [23].

In summary, evidence from a randomized controlled trial has shown that in the treatment of hyperphosphatemia, the use of sevelamer compared with calcium acetate moderates valvular and vascular calcification [20,21], a known risk factor in nonuremic individuals and shown to be a strong predictor of cardiovascular and all-cause mortality in ESRD [18,28]. Because long-term follow-up data are not yet available, understanding the implications of this physiologic effect from a clinical and economic perspective requires predictive equations. Development of such a model cannot wait for the accumulation of follow-up data because payers and policymakers must decide today whether or not to make this binder available and individual physicians must make treatment decisions based on the available evidence. Although subject to the uncertainties inherent in modeling long-term outcomes based on limited short-term clinical trial results, the results of this study suggest that sevelamer should be considered a desirable approach to treating hyperphosphatemia in patients on hemodialysis and 1 year of treatment with sevelamer provides good value for money.

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